ASSOCIATION BETWEEN MORBIDITY AND PHYSICAL ACTIVITY AMONG 18-MONTH-OLD MALAWIAN TODDLERS

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1. Abstract

Introduction

Physical activity is one of the basic needs for toddlers because it can been shown to potentially benefit children's physical, social and cognitive growth. Acute diseases are very common among toddlers, especially in Sub-Saharan Africa. The purpose of this study was to compare activity of healthy and acutely ill toddlers.

Methods

This study was a secondary analysis of the iLiNS-DOSE trial, which took place in Malawi during 2009-2012. The ActiGraph GT3X+ accelerometer was used to measure physical activity. Morbidity measurements were collected into a form by a research assistant together with a guardian's verbal report, based on the already filled Morbidity calendar. Days during which a child was suffering from any symptoms of diarrhoea, fewer or acute respiratory infection were counted as sick days. The main activity outcome was mean vector magnitude accelerometer counts/15s. The secondary outcome was % time spent in moderate-to-vigorous physical activity by the vertical axis. We compared the activity of a sick day and a healthy day in within-children and between children.

Results

Altogether 1 932 participants were enrolled in the iLiNS-DOSE study, 279 children were included in this sub-study and contributed to 843 (41%) days with symptoms (297 participants of within-children and between-children analyses and 729 participants of all healthy or sick during the measurement week analyses). We found the mean accelerometer counts on the within-children analysis in healthy days 303, SD 67 and on days with symptoms 305, SD 70 (difference 2, 95% Cl -6 to 3, p=0.48). The mean accelerometer counts on between-children analysis in healthy days 305, SD 79, and on days with symptoms 303, SD 76, (difference - 2, 95% Cl -4 to 10, p=0.43).

Conclusion

No difference was found in physical activity between days with acute diseases and days without symptoms among Malawian toddlers.

2. Introduction

2.1. Toddlers' physical activity

Physical activity is one of the basic needs for toddlers and it can potentially benefit children's physical, social and cognitive growth (Barros et al. 2010; Ginsburg et al. 2007; Milteer et al. 2012). Children aged one to three years are referred colloquially as toddlers (Bauman et al. 2012). Toddler stage begins by learning how to walk around the one year mark (Bauman et al. 2012; Worobey et al. 2009). Toddlers' physical activity is considered as being naturally spontaneous and based on motivation to explore the surrounding environment (Bauman et al. 2012; Worobey et al. 2009). It includes unstructured activity, like playing (Cliff et al. 2009). The act of playing is a valuable tool through which toddlers explore their surroundings (Ginsburg et al. 2007; Angulo-Barroso et al. 2011). Through playing, children also learn social, cognitive as well as fine and gross motor skills. (Ginsburg et al. 2007; Angulo-Barroso et al. 2011) The brain neurogeneses and synapsegeneses is rapid during childhood (Grantham-McGregor et al. 2007). This development is affected by environmental stimuli (Grantham-McGregor et al. 2007). Playing and spontaneous, unstructured physical activity gives children environment stimuli (Milteer et al. 2012).

Physical activity of toddlers is affected by; environment, social bonding with mother and other family members, nutritional status and natal status (Barros et al. 2010; Hinkley et al. 2008; Milteer et al. 2012; Olney et al. 2007). Factors affecting toddlers' activity are diverse, ranging from biological and genetical to cultural, which can, for example, be seen affecting the diurnal rhythm (Angulo-Barroso et al. 2011; Bauman et al. 2012; Kelly et al. 2006). Angulo-Kinzer et al. found that iron deficiency anemia reduced motor activity during the waking hours in children aged between 6 and 18 months. They also found that the magnitude of difference on physical activity during the waking hour increased in infants with iron deficiency anemia compared to infants without iron-deficiency anemia at 12 and 18 months (Angulo-Kinzer et al. 2002). School aged children are more susceptible to the influence of their parents and peers, in their attitude towards physical exercise, in conjunction with environmental factors, whereas toddlers' activity comes more from their natural desire to explore (Bauman et al. 2012; Hinkley et al. 2008; Sallis et al. 2000; Sandercock et al. 2010). On the other hand, there is evidence that social interaction and maternal-child bond plays an important role on the physical activity levels in the early age of the childhood physical activity (Hnatiuk et al. 2013).

Several guidelines can describe physical activity for the early years in childhood. The National Association for Sport and Physical Education (NASPE) in the US has developed Active Start Guideline for children aged zero to five. According to the guideline's recommendation, toddlers should take part in 30 min of organised activity and 60 min or more of unorganised activity every day. (NASPE 2009) Guidelines for Australia and United Kingdom for physical activity for zero to five years old children recommend at least 180 min of activity spread throughout the day. At the early years the activity is more unstructured through playing, while for older children activity should be more structured and organised. (Commonwealth of Australia, Department of Health and Ageing 2010; UK Department of Health 2011)

Younger children's daily activities appear to be more in line with the guidelines than that of preschool aged children. Hnatiuk et al. studied the physical levels of 19-month-old toddlers and among them 90,5% of the toddlers met the current Australian Physical recommendations for zero to five-year-olds (Hnatiuk et al. 2012). On the other hand, Hinkley et al. studied the physical level of preschool age children and among them only 5% met the current Australian Physical recommendations for zero to five-year-olds (Hinkley et al. 2012; Hnatiuk et al. 2012). A systematic review of physical activity by Tucker et al. reporting physical activity levels of any intensity among two to six years concluded that only 54% of the studied children met the NASPE's physical activity recommendation (Tucker et al. 2008).

2.2. Morbidity of children under five years of age

Globally, low respiratory infection, diarrhoea and malaria are common among children under five years of age (Rudan et al. 2005). In 2010, estimated number of disability-adjusted life years (DALYs) lost to malaria was 57 162 000, diarrhoeal diseases 30 435 500 (DALYs) and lower respiratory infections, meningitis, and other common infectious diseases 84 747 000 (DALYs) in the Sub-Saharan Africa. (Institute for Health Metric and Evaluation, IHME) Malawi's fight against malaria, tuberculosis and HIV along with other tropical diseases is an on-going affair. The incidence of malaria was 28 872/ 100 000/year, prevalence of tuberculosis was 164/100 000 and prevalence of HIV was 5 904/100 000 in 2012. (WHO 2013)

Malaria is caused by protozoa called *Plasmodium*, which is transmitted by female *Anopheles* mosquito (Lopez del Prado et al. 2014; White et al. 2014). There are five Plasmodium species causing malaria to humans: *P. falciparum*, *P. Vivax*,, *P. Ovale*, *P. Knowlese* and *P. Malaria* (Lopez del Prado et al. 2014;White et al. 2014). Of those *P. falciparum* and *P. Vivax*, are most common and *P. falciparum* causes most severe illnesses (Lopez del Prado et al. 2014). Symptoms of malaria can vary from mild symptoms to severe malaria. Symptoms of uncomplicated malaria can be vague, including muscle aches, fatigue, abdominal discomfort, headaches and often nausea, vomiting and diarrhoea and periodic fever. (Lopez del Prado et al. 2014; White et al. 2014) Symptoms of severe malaria include severe anaemia and hypoglycaemia and are most common in children (White et al. 2014). The first-line treatment for uncomplicated malaria is Artemisinin combinations (White et al. 2014).

Review of the effects of malaria on cognition found that malaria affected negatively many areas in child's development, such as visuo-spatial skills, memory and languages skills (Kihara et al. 2006). The effects are not caused only by severe cerebral malaria, even less severe malaria can result in reduced cognitive skills (Kihara et al. 2006). Severe malaria episodes are associated with malnutrition, absence of schooling and low socio-economic status, which also can cause neurological impairments (Kihara et al. 2006).

Diarrhoea is usually a symptom of an infection in the intestinal track by bacteria, viruses or parasites (WHO, Fact sheet N:330: diarrhoeal diseases) The most common viral diarrhoea are *rotavirus* and *adenovirus*, bacterial are *Entero Coli*, *Salmonella Enterica*, *Shigella*, *Cambylobacteria* and for parasites *Entamoeba histolytica*, *Trichomonas intestinalis*, *Giardia lamblia* and *Cryptosporidiosis* (Bonkoungou et al. 2013; Kotloff et al. 2013). Definition of diarrhoea is the passage of three or more loose or liquid stool per day (WHO, Fact sheet N:330: diarrhoeal diseases). The prevention and treatment of diarrhoea includes maintaining good hygiene, adequate sanitation and rehydration with Oral rehydration solution (ORS), zinc supplements, continued feeding and antibiotics for bloody diarrhoea (Das et al. 2014)

Respiratory infections are caused by bacterial, viral or mixed organisms. Bacterial infections are most commonly caused by *Streptococcus Pneumoniae* and *Hemophilius Influenzae* and viral infections by *respiratory syncytial virus* (RSV), *parainfluenza viruses*, *influenza virus*, and *human metapneumovirus* (hMPV). (Cashat-Cruz et al. 2008; Litwin et al. 2014) The symptoms of respiratory infections vary from mild illness to severe pneumonia: cough, tachypnoea (rapid breathing), dyspnea (difficult breathing), runny nose and fever (Hoffman et al. 2012). The prevention of acute respiratory infection includes oral rehydration, immunisations against pneumococcus and *H. influenzae,* breast-feeding and improved nutrition, like vitamin A supplementation (Cashat-Cruz et al. 2008). The treatment of respiratory infection is based on the severity of diseases: from relieving symptoms to antibiotics and intensive care (Cashat-Cruz et al. 2008).

In addition to infectious diseases, malnutrition is also prevalent in Malawian children. According to Government of Malawi, stunting (low height-for-age, HAZ) was more common than wasting (low weight-for-age, WAZ). 16,7% of children less than five years of age were underweight (WAZ < -2SD), 42.4% of children were stunted (HAZ < -2SD) and 16.3% severely stunted (HAZ < -3SD) in 2012 (Government of Malawi, MDG end line MICS Survey, 2014). Recent survey by National Statistical office in Malawi reported the prevalence of symptoms in children under the age of five within the previous two weeks: fever 37,2%, diarrhoea 24,1% and acute respiratory infection (ARI) 7,8% (Government of Malawi, MDG end line MICS Survey, 2014). Seasonal peaks of diarrhoea, malaria and respiratory infection have been observed in Malawi. During the rainy months, diarrhoea and malaria were more prevalent whereas respiratory infections peaked in the cold season. (Vaahtera et al. 2000)

It is noteworthy that malnutrition is a risk of infection (Schaible et al. 2007). Having several diarrhoea and fever episodes during childhood increases the risk of stunting (Black et al. 2013; Checkley et al. 2008; Dewey et al.2011). Incidence of diarrhoea peaks at 6-11 months at the time when a child learns to crawl and the complementary feeding starts (Dewey et al. 2011). Risk of stunting is increased if diarrhoea episodes are severe and persistent (Dewey et al. 2011).

Infections may affect appetite. There is no evidence of decrease in appetite during a respiratory infection. Respiratory infection with fever has a similar kind of effect as diarrhoea on growth. (Black et al. 2013; Dewey et al. 2011) Fever activates the immune system which in turn suppresses appetite and reduces growth (Dewey et al. 2011). Other infectious diseases, like measles, malaria and meningitis can lead to acute wasting and can have long-term effects on linear growth (Black et al. 2013).

2.3. Physical activity and morbidity

Many studies have investigated what effects physical activity has on non-communicable diseases and general well-being of children (Dencker et al. 2008; Janz et al. 2005; Koehmoos et al. 2011; Msyamboza et al. 2011; Pradinuk et al. 2011; Sääkslahti et al. 2004). Physical activity in early childhood can have positive effect on bone mineralization as well as lower the risk of cardiovascular diseases (Janz et al. 2005; Sääkslahti et al. 2004). A systematic review of physical activity and health in 0 - 4 years evaluated relationship between physical activity and adiposity measures, bone and skeletal health, motor skill and cognitive development, psychosocial health and cardiometabolic health indicators in infants, toddlers and preschoolers (Timmons et al. 2012). In toddlers, the study found moderate evidence to suggest that higher physical activity was positively associated with bone and skeletal health (Timmons et al. 2012).

Some studies have focused on the effects of chronic diseases on physical activity (Table 2.1). The findings suggest that children with chronic disease, chronic pain or cancer are less active than healthy children (Banks et al. 2012; Huang et al. 2010; Durstine et al. 2000; Long et al. 2008; Pan et al. 2007; Sundberg et al. 2012; Winter et al. 2010). However, one study did not to find any differences in activity in children with long-term disease as compared to healthy children (Rintala et al. 2011).

Table 2.1. Previous studies on association between physical activity and morbidity

Publication/ Country	Participant: N/ age	Sickness/ Impairment	Method/Outcome measures	Results
Banks et al. 2012, Canada	History of KD: 27; male 20 and female 7/ 11+/-3 years old Population based data the Canadian Health Measures Survey	Kawasaki disease (KD)	KD activity data (accelerometer) were compared with a population -based study of healthy children/ MVPA	Patient with KD performed less MVPA than healthy children Males with KD 27 min/ d Males without KD 61 min/d, P < .001 Females with KD 10 min/d Females without 47 min/d, P < .001.
Long et al. 2008,	40 adolescents (20 with chronic pain and 20 healthy)/ 12-17 years	Chronic pain	Questionnaires regarding pain, activity limitation and depression. Activity levels were determinate using Actiwatch 64 -device for 7 days/ MVPA (≥ 30 min/ day) sedentary activity	Physical activity was lower in adolescents with chronic pain than in healthy peers. Adolescents without chronic pain achieve ≥30 min of MVPA on 3.29 days/ week (95% Cl 2.17 - 4.48) Adolescents with chronic pain achieve of MVPA on ≥30 min 1,6 days/ week (95% Cl 0.70 - 4.20)
Rintala et al. 2011, Finland/ Canada	2720 Canadian and 3459 Finnish pupils / 13.5-15.5 years	Long-term illness or disability -cerebral palsy -diabetes -arthritis -allergy -epilectic seizures - difficulty to see, hear, speak, move, breath	Self-reported MVPA, average days per week (95% Cl)	No difference on activity with or without long-term disabilities Canada With long term illness on MVPA/days Boys 4.37 (95% Cl 4.12 - 4.62) n= 211 Girls 4.10 (95% Cl 3.89 -4.31) n= 290 Without long term illness on MVPA/ days Boys 4.65 (95% Cl 4.53 - 4.77) n= 959 Girls 3.95 (95% Cl 3.85 -4.06) n= 1128 Finland With long term illness on MVPA/ days Boys 3.69 (95% Cl3.48 -3.91) n= 297 Girls 3.40 (95% Cl3.21 - 3.59) n=336 Without long term illness on MVPA/ days Boys 3.64 (95% Cl3.54 -3.73) n= 1401 Girls 3.28 (95% Cl3.18 - 3.38) n= 1347
Olney et al. 2008, Zanzibar, Tanzania	771 Zanzibarian children/ 5 -19 months Nonmovers, n: 162; crawlers, n:147; walkers, n:388; all children, n: 697	Malaria	Observations of children's motor activity (2- 4 h) in and around their homes / Total motor activity (TMA) and locomotion (% spend time in locomotion)	Malaria infection sig. predicted less TMA and locomotion in crawlers, not in walkers. (no data found) Children with 1–999 parasites/mL blood spent 12% less time, Children with 1000–4999 parasites/mL blood spent 42% less time, Children with over 5000 malaria parasites spent 60% less time, than children without any parasites.

Table 2.1. Previous studies on association between physical activity and morbidity

Publication/ Country	Participant: N/ age	Sickness/ Impairment	Method/Outcome measures	Results
Pan, 2008, Taiwan	7-12 years ASD: 23 boys and 1 girl Early Primary, n= 12 Late primary, n=12 Non-ASD: 23 boys and 1 girl Early primary, n=12 Late primary, n=12	Autism spectrum disorder (ASD)	5 days use of accelometer (MVPA)	Children with ASD were less activity that children without disabilities. ASD: Early primary MVPA(min) 24.12 ± SD 7.75 ASD: Late primary MVPA(min) 31.03 ± SD 10.31 Non-ASD: Early primary MVPA(min) 35.62 ± SD 10.32 Non-ASD: Late primary MVPA(min) 34.47 ± SD 10.65
Sundberg et al. 2012, Sweden	24 children (12 girls) with type 1 diabetes mellitus and 26 (14 girls) healthy controls/ under 7 years	Diabetes Mellitus	7 days use of accelerometer or heart rate registration / MVPA (min) and total PA	Children with type 1 diabetes had sig. lower activity than healthier peers. Time spent in MVPA differed by 11 min⁄d between groups, p = 0.027

Abbreviations: MVPA, percentage of time spent in moderate to vigorous activity; Cl, confidence interval KD, Kawasaki diseases; TMA, Total motor activity; ASD, Autism spectrum disorder

Acute diseases are very common in toddlers (Rudan et al. 2005) However not many studies have focused on the effects of acute diseases on physical activity. One observational study on 5 - 19 month-old Zanzibari was found. The study assessed anemia, iron deficiency, hemoglobin (Hb), length-for-age Z-score (LAZ), and malaria infection as predictors of motor activity. Motor activity was observed by trained observers conducted 2- to 4-h observations in and around childrens' homes. The study deduced that malaria infection decreased the time spent in motor activity among the crawlers. Iron deficiency anemia predicted less activity in walkers. (Olney et al. 2007)

3. Aims

The aim of the study was to test a hypothesis that children are less active on the days when they have parental reported acute illness than on the days that they are reportedly healthy. This was done by comparing physical activity of 18-month-old toddlers on days with and without any symptoms and comparing physical activity on days with fever, diarrhoea or ARI separately and without any symptoms.

4. Methods

4.1. Settings

This study was a secondary analysis of data collected in the iLiNS-DOSE (Prevention of Linear Growth Failure in Infants and Young Children With Lipid-based Nutrient Supplements trial). The iLiNS-DOSE concentrated on alternative doses and composition of LNS (lipid-based nutrient supplements) and their connection to infants' linear growth between 6 and 18 months of age.

1932 infants met the set criteria for the iLiNS-DOSE trial and were randomised into six different intervention groups. One of the groups was control group and five were intervention groups. Children in the intervention groups were given differing quantities of milk containing LNS or milk free LNS. The main aim of the study was to assess the effect of LNS on children's linear growth.

Study site was situated in Malawi, Mangochi District and included two sites, semi-urban area served by Mangochi district hospital and a rural area served by Namwera health clinic. More information about iLiNS-DOSE trial can be found at www.ilins.org.

4.2. Participants

All participants of iLiNS-DOSE trial were invited in this sub-study. We included all participants whose guardians gave verbal consent to participate in the activity sub-study. We excluded those who did not have enough either ActiGraph or morbidity data. Minimum of two days of data were considered as sufficient amount of ActiGraph data.

4.3. Activity measurement

Physical activity was measured with the ActiGraph GT3X+ accelerometer (ActiGraph Ltd., Pensacola FL, USA). It is a small, tri-axial accelerometer, measuring 4,6 cm x 3,3 cm x 1,5 cm and weighing 19 g. It records accelerations on three different axes: vertical, anteroposterior and mediolateral (John et al. 2012). During the clinic visit, a research assistant introduced the ActiGraph to the guardian who were then advised how to secure the device on the child's right hip using an elastic band. The accelerometer was to be worn day and night continuously, only to be removed if the child displayed any symptoms of discomfort. After measurements had concluded, a research coordinator

downloaded and processed the raw accelerometer data using ActiLife software.

4.4. Morbidity measurement

Morbidity measurements were collected by a research assistant together with a guardian's verbal report. The guardian had filled out the morbidity calendar (appendix 4.2.) during the week. The research assistants filled in the morbidity form, (appendix 4.1.) based on both the morbidity calendar and the guardian's verbal report at the end of week. The morbidity form included information of child's symptoms on each day. If the calendar had not been filled in or there were any discrepancies between the interview and the markings in the morbidity calendar, the guardian's verbal report was be taken as truth and recorded in.

For the purpose of this analysis, we grouped guardian-reported to following symptoms. (Table 4.4.)

Table 4.4. Definition of symptoms

Symptom	Defination of symptom
Stool	Number of loose stool, which is more watery than normal for particular child
Fever	Feeling by hand or measured the body temperature to be higher than normal
Cough [1]	Subjectively
Rapid breathing [1]	The respiratory rate is higher than normal
Difficult breathing [1]	Child's chest in-drawings, nasal flaring or laboured or noisy breathing
Nasal discharge [1]	Runny or purulent fluid from the nose

[1] Grouped together as acute respiratory infection (ARI)

4.5. Other outcome measurements

Children's date of birth was obtained from individual health booklets (passports) issued by the health services for recording demographic and health information including immunisations and growth. The children were weighted and their length was measured by the research assistants at the clinic visit when the activity measurement started. Research assistants interviewed the guardians in order to obtain mother's age, education, number of children under five living in the household and number of naps children took during the day. Research assistants also observed the children to assess their ability to walk. Guardians were also asked whether their children were being carried on five situations (when on the way to the market, fetching water, on the way to the field, visiting neighbours and other). We calculated a carrying score by totalling the 'yes' answers.

4.6. Data processing and analyses

Data were analysed using Stata/IC software, version 12.1. (StataCorp, College Station, TX, USA). The level of statistical significance was set at 0.05 for all analyses. Raw accelerometer data was changed in ActiLife - software into 15 s epoch in .csv format and then read in Stata. Night time was removed from the output. First and last days of measurements were excluded because they were incomplete days. A day was deemed valid if it had a minimum of six hours of accelerometer data between 5:00 am and 8:00 pm, after excluding strings of zero counts of 20 minutes or more. Minimum of two days of data was deemed sufficient, because this sub-study compared activity between days with and without symptoms. We used daily mean accelerometer counts/15s as the main outcome (Reilly et al. 2008; Kim et al. 2014). The accelerometer data was changed into vector magnitude (VM) counts, which were calculated by taking square root of the sum of squared activity counts of each axis. The secondary outcome was percentage of time spent in moderate-to-vigorous physical activity (MVPA) by the vertical axis. % of time in MVPA was calculated using validated cut points of 418 counts/15s (Trost et al. 2012).

Morbidity data was double entered into excel sheet for each day. Days during which a child was suffering from any symptoms of diarrhoea, fever or acute respiratory infection (ARI) were counted as sick days.

Children with valid activity data from at least one healthy and one sick day were included in the main analysis. Children with all healthy days or all sick days were included in the secondary analysis. T-test, Fisher's exact and one-way analysis of variance (ANOVA) tests were used to test differences between the included group, the excluded group and the group with all sick days or all healthy days.

1) We used paired T-test for within-children analyses to assess test differences in physical activity between healthy days and days with symptoms (any symptom or symptoms of ARI, fever and diarrhoea).

2) We used unpaired T-test for between-children analyses to assess test the differences in physical activity between healthy days, days with symptoms (any symptom or symptoms of ARI, fever and diarrhoea).

3) We used unpaired T-testing for the differences in physical activity between children who had all healthy days or all days with symptoms (any symptom or symptoms of ARI, fever and diarrhoea).

The sample size, 92 for this sub-study. It offered 90% power at statistical significance level of 5% for rejecting the null hypothesis. Null hypothesis of study was that there is no difference in activity between healthy days compared to sick days.

5. Results

From the 1 932 participants enrolled to the iLiNS-DOSE study, 451 were lost to follow-up, 79 died before they became 18 months old and 57 refused the activity measurements (Figure 5.1.). Consequently, 1 345 participants took part in the activity measurements. Of these, 239 had insufficient accelerometer data or missing morbidity data and 80 had either unusable or lost accelerometer data. Of the 1 026 participants (53% of the original iLiNS-DOSE cohort), 297 had both sick and healthy days, 118 had no reported healthy days and 611 had no reported sick days during the activity measuring week.

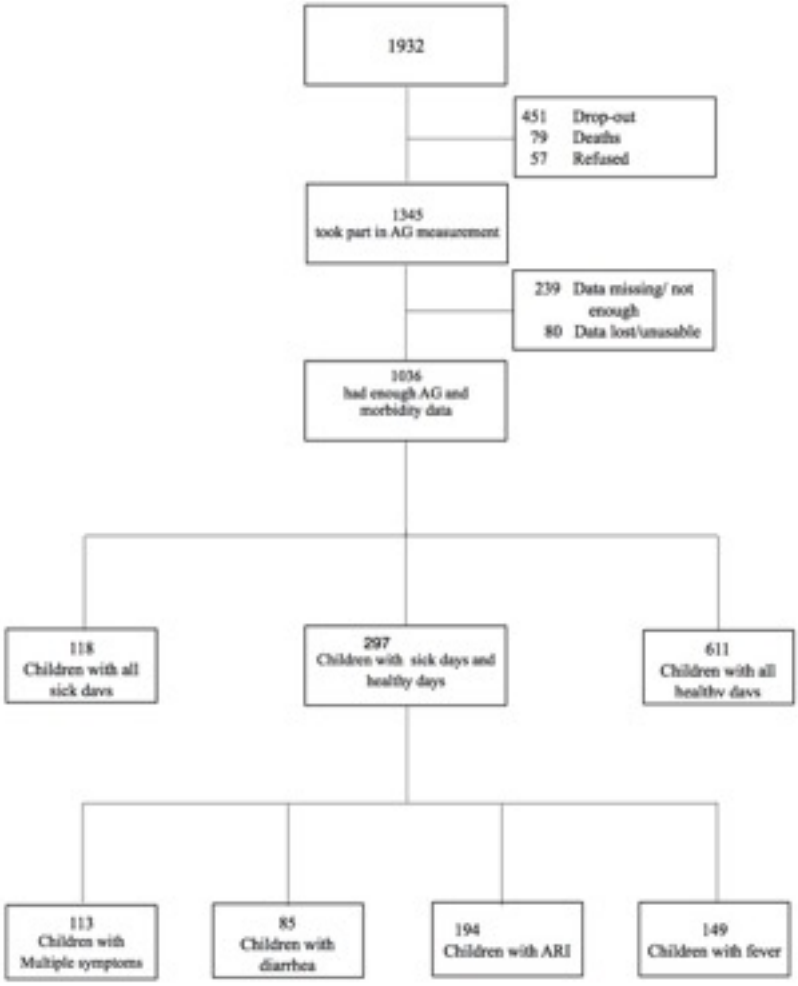

Figure 5.1: Participant flow.

Table 5.1. Background characteristics of participants at 6 months and at the time of physical activity measurements

Variables	Included	Activity measured but all sick days or all healthy days	Excluded before measurements or not enough activity measurements or missing morbidity data	P-value
Number of Children	297	729	906	N/A
Male, n (%)	145 (49%)	372 (51%)	452 (50%)	0.78 (Fisher's exact test)[1]
Mother's age, mean (SD)	27 (7)	27 (6)	26 (6)	0.001 (ANOVA)[1]
Mother's education, completed years of school, mean (SD)	4.2 (3.6)	4.5 (3.6)	5.0 (3.5)	0.01 (ANOVA)[1]
Children under 5-years old in family, mean (SD)	1.7 (0.7)	1.6 (0.7)	1.6 (0.7)	0.64 (ANOVA)[1]
Situation at 18 months, substudy enrolment				
Age (month), mean (SD)	17.9 (0.3)	17.9 (0.4)	N/A	0.91 (t-test)[2]
WLZ, mean (SD)	-0.23 (1.0)	-0.28 (1.0)	N/A	0.52 (t-test)[2]
LAZ, mean (SD)	-1.9 (1.1)	-1.8 (1.1)	N/A	0.79 (t-test)[2]
Walks without support (%)	273 (92%)	667 (91%)	N/A	0.07 (Fisher's exact test)[2]
Naps during day, mean (SD)	1.4 (0.8)	1.4 (0.7)	N/A	0.003 (t-test)[2]
Carrying Score, mean (SD)	2.5 (1.3)	2.4 (1.4)	N/A	0.03 (t-test)[2]

Abbreviations: SD standard definition; WLZ weight-for-length Z-score; LAZ length-for-age Z-score

1 ANOVA's and Fisher's exact tests were used to test p-values between all three groups.

2 T-test's and Fisher's exact tests were used to test the p-values between the first two groups.

The background characteristics for the all healthy or all sick group and the excluded group were otherwise similar to the main analysis group, except for small differences in maternal age and maternal education (Table 5.1.).

The background characteristics for the children how where either sick or healthy during the whole measurement week are shown Table 5.2. The children were sick with during the whole measurement week took more naps and were carried more than children without any symptoms.

Table 5.2. Background characteristics of children who had either healthy or symptom days

Variables	All healthy children	All sick children	P-value
Number of children (n)	611	118	
Male (%)	307 (50)	65 (55)	366
LAZ, mean (SD)	-1.84 (1.09)	-1.81 (0.95)	0.79
Naps during day, mean (SD)	1.35 (0.66)	1.56 (0.80)	0.03
Carrying Score, mean (SD)	2.36 (1.37)	2.67 (1.41)	0.03

Abbreviations: SD standard deviation; LAZ length-for-age Z-score

The 297 children included in the main analyses contributed to 843 days with symptoms (41% of all days) and 1234 days without symptoms (Table 5.3.). Acute respiratory infection was the most common symptom, reported by 363 guardians (43%).

Table 5.3. Number of days different symptoms

Symptoms	Number of days
Total, n	2077
None of symptoms, n	1234 (59% of all days)
Any symptoms, n	843 (41% of all days)
ARI[1], n	363 (43% of all symptoms days)
ARI[1] and fever, n	170 (20% of all symptoms days)
Fever, n	145 (17% of all symptoms days)
Diarrhoea, n	110 (13% of all symptoms days)

Table 5.3. Number of days different symptoms

Symptoms	Number of days
Diarrhoea, fever and ARI[1], n	24 (2,8% of all symptoms days)
ARI[1] and diarrhoea, n	16 (1,9% of all symptoms days)
Diarrhoea and fever, n	15 (1,8% of all symptoms days)

Abbreviations: ARI acute respiratory infection

[1] ARI was defined as the child having at least two out of the following symptoms:rapid or difficult breathing, nasal discharge and cough.

The within-children comparison of mean accelerometer counts and % of time in MVPA between the healthy days and days with symptoms are presented in Figure 5.4. and Table 5.4. The mean (SD) VM counts/15s for the healthy days was 303 (67) and for days with symptoms 305 (70) (P=0.48). The mean values for all different symptoms are shown in Table 5.4. The mean activity of the children were mostly less on healthy days than on days with symptoms, but the differences were not statistically significant.

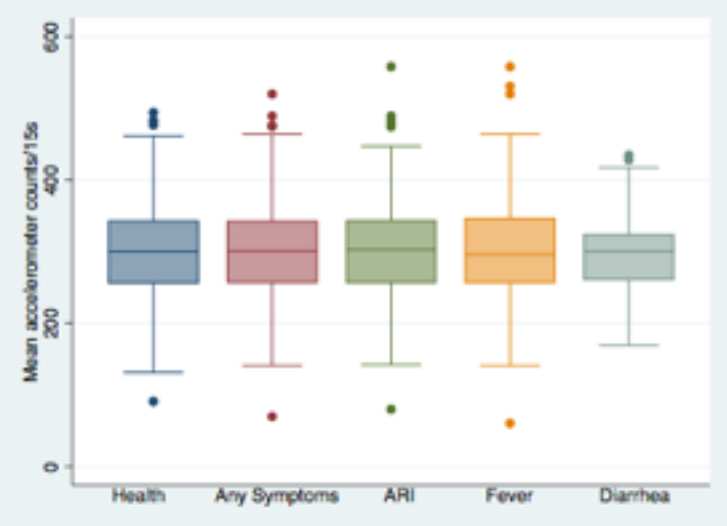

Figure 5.4: Box-Whisker plots of mean accelerometer counts/15s for days with different symptoms in within-children analysis. Boxes indicate the upper and lower quartiles of activity counts, lines indicate median counts, whiskers span over data points that are within 1.5 IQR of the nearer quartile, outliers are individually marked.

Table 5.4. Physical activity in the days with different symptoms as compared to healthy days, within-children analysis (paired T-test)

	Child with any symptoms n= 297	Child with ARI n= 194	Child with fever n= 149	Child with Diarrhoea n= 85	Child with ARI and fever n= 89
Healthy child mean (SD), VM counts/ 15s for healthy days	303 (67)	302 (67)	304 (71)	297 (57)	293 (68)
Mean (SD), VM counts/ 15s for days with symptoms	305 (70)	305 (70)	304 (70)	294 (56)	300 (78)
Difference (95% CI) between the symptom and the healthy days	-2 (3 to -6)	-3 (3 to -9)	-0.4 (6 to 8)	3 (13 to -7)	-6 (5 to -18)
P-value	0.48	0.26	0.93	0.52	0.27
Healthy child, mean % of time in MVPA (SD), vertical axis	12.1 (4.9)	11.9 (4.8)	12.7 (5.0)	11.8 (3.8)	12.0 (5.0)
Mean % of time in MVPA (SD), vertical axis	12.2 (4.7)	12.1 (5.0)	12.8 (5.9)	11.4 (3.6)	12.6 (5.9)
Difference (95% CI) between the symptoms and the control group	-0.1 (0.3 to -0.5)	-0.2 (0.3 to -0.7)	-0.1 (0.6 to -0.8)	0.3 (1.2 to -0.5)	-0.7 (0.3 to -1.7)
P-value	0.57	0.37	0.67	0.44	0.19

Abbreviations: VM, vector magnitude; SD standard deviation; MVPA, percentage of time spent in moderate to vigorous activity; CI, confidence interval;

The distribution of mean VM accelerometer counts on days with different symptoms in the between-children comparison is shown in Figure 5.5. and Table 5.5. The mean (SD) VM counts/15 s for the healthy days for all children was 305 (79) and days with any symptoms 303 (76). The mean VM counts and % of time in MVPA for days with different symptoms are shown in Table 5.5. In the between-children analysis, the point estimate for activity was slightly greater on healthy days than on days with any symptoms but the differences were mostly not statistically significant. We found a significant difference in mean VM counts between healthy days and days with diarrhoea (difference -15, 95% Cl 29 to 2) and days with ARI and fever (difference -13, 95% Cl 26 to 0.9).

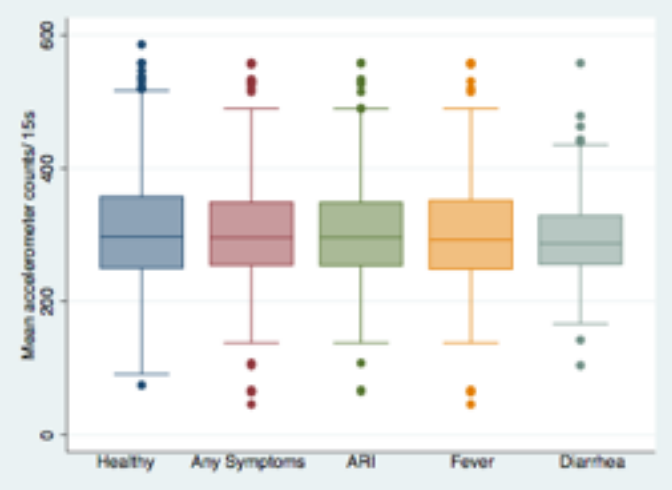

Figure 5.5: Box-Whisker plots of mean vector magnitude accelerometer counts/15 s for days with different symptoms in between-children analysis. Boxes indicate the upper and lower quartiles of activity counts, lines indicate median counts, whiskers span over data points that are within 1,5 IQR of the nearer quartile, outliers are individually marked.

Mean % of time spend in MVPA (SD) for healthy days for all children was 12.3% (5.9) and for sick days 12.1% (5.7). The mean percentage values for the different symptoms in the between-children comparison are shown in Table 5.5. The point estimates for mean % time spend in MVPA were mainly greater on healthy days than on days with symptoms. However, the differences were not statistically significant.

Table 5.5. Physical activity in the different symptom groups, between-children analysis (unpaired T-test)

	Control, Healthy days (n=1234)	Days of any Symptom (n=843)	Days with ARI (n= 363)	Days with fever (n= 145)	Days with diarrhoea (n=110)	Days with ARI and fever (n=170)
Mean (SD),VM counts/ 15s	305 (79)	303 (76)	302 (75)	300 (83)	290 (62)	292 (80)
Difference (95% CI) between the symptoms and the control group		-2 (10 to 4)	-3 (11 to -5)	-5 (15 to -5)	-15 (29 to 2)	-13 (26 to 0.9)
P-value		0.43	0.45	0.31	0.02	0.04

Table 5.5. Physical activity in the different symptom groups, between-children analysis (unpaired T-test)

	Control, Healthy days (n=1234)	Days of any Symptom (n=843)	Days with ARI (n= 363)	Days with fever (n= 145)	Days with diarrhoea (n=110)	Days with ARI and fever (n=170)
Mean % of time in MVPA (SD), vertical axis	12.3 (5.9)	12.1 (5.7)	11.9 (5.6)	12.5 (6.2)	11.3 (4.3)	12.0 (6.0)
Difference (95% CI) between the symptoms and the control group		-0.1 (0.6 to -0.4)	-0.4 (0.9 to 0.2)	0.3 (0.5 to -1.0)	-1.0 (1.9 to -0.1)	-0.3 (1.2 to -0.7)
P-value		0.66	0.23	0.47	0.08	0.55

Abbreviations: VM, vector magnitude; SD standard deviation; MVPA, percentage of time spent in moderate to vigorous activity; CI, confidence interval;

The mean physical activity was compared also between those children, who were all healthy and those who were all sick during the measurement week. The mean VM counts/15s for healthy children was 310 (SD 80) and for children with symptoms 295 (SD 76) (difference 15, 95% CI 9.0 to 21). The difference was statistically significant $p<0.0001$. The mean % of time in MVPA for healthy children was 12% (SD 0.1) and for sick children with symptoms 12% (SD 0.2) [difference 0.4, 95% CI -0.04 to 0.8), $p=0.08$].

6. Discussion

The aim of this study was to assess the association between morbidity and physical activity among 18-month-old Malawian toddlers. The study found that physical activity in within-children comparison was not statistically different on healthy days than on the days with symptoms. The results of between-children analysis were mainly similar, except for children having less VM counts on days with diarrhoea or symptoms of acute respiratory infection and fever than on days without any symptoms. Furthermore, children who were ill for the entire measurement week expressed less activity than children who were healthy during the whole measurement week.

The main strengths of this study were the objectively measured physical activity and strong statistical tests employed. Accelerometers are objective methods to measure physical activity (Reilly et al. 2008; Ward et al. 2005) and they have shown to be a valid method assessing physical activity among toddlers (Pulakka et al. 2013; Trost et al. 2012) Accelerometers enable detecting small changes in physical activity between days (Jonh et al. 2012; Cliff et al. 2009) For analyses we used both the paired t-test and unpaired t-test. The paired t-test controls for the confounding, time invariant, background characteristics by comparing different days of the same individual. On the other hand, unpaired t-test is comparing different individuals and the background characters are not controlled for. (Allison, 2005)

The main weaknesses of this study were subjective evaluation of morbidity data, relatively short measurement period and limitations related to the accelerometer measurement. Subjectively collected measurements, like the morbidity data in this study, always have the possibility for bias, either reporting or recall bias. However, we clearly defined the symptoms for the guardians to minimise reporting bias. Furthermore, we used a morbidity calendar which was filled in daily by the guardians to minimise recall bias. Accelerometer methods have their limitations. Accelerometers are only able to detect movement of the body part where they are attached to (Reilly et al. 2008; Ward et al. 2005). Moreover, accelerometers do not detect when the child is being carried.

As a limitations the results of this study cannot be generalised outside the context of toddlers in Sub-Saharan Africa. Typical for this context is high prevalence of malnutrition, which can have an impact on physical activity and morbidity (Black et al. 2013; Schaible et al. 2007). Another feature of this context is high incidence of certain diseases like malaria, which are not common in other

parts of the world.

Although some studies have assessed the association between chronic diseases and physical activity (Banks et al. 2012; Huang et al. 2010; Durstine et al. 2000; Long et al. 2008; Pan et al. 2007; Rental et al. 2011; Sundberg et al. 2012; Winter et al. 2010), there is a paucity of studies investigating physical activity during an acute illness. One study was found comparing the effects of acute diseases and motor activity among Zanzibari children aged 5 - 19 months (Olney et al. 2007). Along the lines of our findings, it found that malaria did not have any effects on the motor activity in those who could walk, although malaria decreased the motor activity in those who crawled (Olney et al. 2007). The comparison was done between all children and between the groups of nonmovers, crawlers or walkers. The age range of children in our study was narrower, 18-months-old, compared to the Zanzibari study age group, where age range was from 5- to 19-months old children. Physical activity was evaluated by observation lasting for 3 - 4 hours by a study assistant in the child's home. The observation is considered less an objective method than accelerometer, which was used in our study to evaluate physical activity (Reilly et al. 2008). In our study, physical activity was evaluated at least during two different days, which allowed for within-children comparison in activity of different days. On the other hand, accelerometers only analyse time spend on different activity intensities, it does not determine the type of activity. For the outcome measurements, the Zanzibari study used total motor activity and locomotion, both of those were sums of time spend on activity during the day. In our study, outcome measurements were total daily activity (daily mean accelerometer counts/15s) and % of time spent in moderate-to-vigorous physical activity. The acute diseases were evaluated objectively, by thick and thin blood films, on the Olney et al. study and our evaluation for the acute diseases were subjectively and based on different clinical symptoms (Olney et al. 2007)

There are several theoretically plausible explanations for lack of association between acute diseases and children's physical activity. This study explored association between acute diseases, which last only a short period of time and physical activity, and the activity measurement was done only for one. It is possible that the mainly short periods of acute diseases observed in this study do not have an impact on children's physical activity. It is also possible that symptoms, fever, ARI and diarrhoea, evaluated in this study, do not reduce activity. On the other hand, the activity of toddlers naturally varies day to day (Bauman et al. 2012).

It is also possible that the acute diseases measured by parental reports do not have any effect on ac-

tivity. Since the morbidity data collection was done via parental reporting, the parents could have reported very mild symptoms as well. Other plausible reason is carrying as a confounder. We were unable to assess carrying time on daily basis, but children with symptoms during the whole measurement week had higher carrying score than children who were all healthy during the measurement week, indicating that there can be more carrying when children are sick. Children with symptoms were carried more than children without symptoms during the measuring time.

In conclusion, we did not find any association between acute diseases and reduced physical activity among Malawian toddlers in the within-children analyses although there was some evidence of reduced activity in the between-children analysis. Children with symptoms during the whole measurement week were less active than children without any symptoms during the week. More research, with longer measurement period and more objective measurement of illnesses, is warranted on role of acute sicknesses in the interplay of different factors that affect physical activity.

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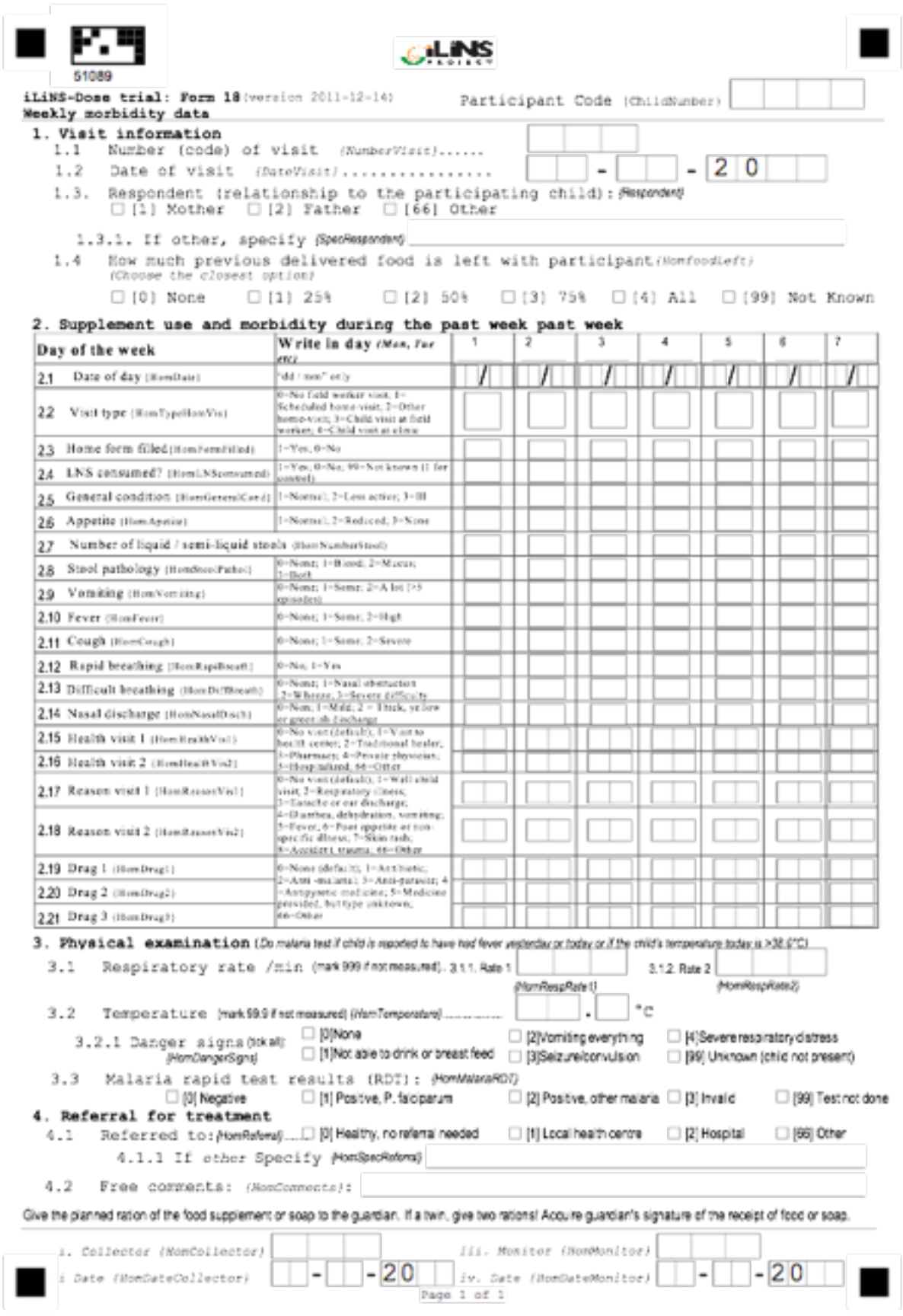
Appendix 4.1. Weekly morbidity form



51089

iLiNS-Dose trial: Form 18 (version 2011-12-14) Participant Code (ChildNumber)

Weekly morbidity data

1. Visit information

1.1 Number (code) of visit (NumberVisit).....

1.2 Date of visit (DateVisit)..... - - 20

1.3. Respondent (relationship to the participating child): (Respondent)

☐ [1] Mother ☐ [2] Father ☐ [66] Other

1.3.1. If other, specify (SpecRespondent)

1.4 How much previous delivered food is left with participant (HomfoodLeft)

(Choose the closest option)

☐ [0] None ☐ [1] 25% ☐ [2] 50% ☐ [3] 75% ☐ [4] All ☐ [99] Not Known

2. Supplement use and morbidity during the past week past week

Day of the week	Write in day (Mon, Tue etc)	1	2	3	4	5	6	7
2.1 Date of day (HomDate)	"dd / mm" only	/	/	/	/	/	/	/
2.2 Visit type (HomTypeHomVis)	0=No field worker visit; 1=Scheduled home visit; 2=Other home-visit; 3=Child visit at field worker; 4=Child visit at clinic							
2.3 Home form filled (HomFormFilled)	1=Yes, 0=No							
2.4 LNS consumed? (HomLNSconsumed)	1=Yes, 0=No, 99=Not known (1 for control)							
2.5 General condition (HomGeneralCond)	1=Normal; 2=Less active; 3=Ill							
2.6 Appetite (HomAppetite)	1=Normal; 2=Reduced; 3=None							
2.7 Number of liquid / semi-liquid stools (HomNumberStool)								
2.8 Stool pathology (HomStoolPathol)	0=None; 1=Blood; 2=Mucus; 3=Both							
2.9 Vomiting (HomVomiting)	0=None; 1=Some; 2=A lot (>5 episodes)							
2.10 Fever (HomFever)	0=None; 1=Some; 2=High							
2.11 Cough (HomCough)	0=None; 1=Some; 2=Severe							
2.12 Rapid breathing (HomRapBreath)	0=No, 1=Yes							
2.13 Difficult breathing (HomDifBreath)	0=None; 1=Nasal obstruction 2=Wheeze; 3=Severe difficulty							
2.14 Nasal discharge (HomNasalDisch)	0=Nom; 1=Mild; 2 = Thick, yellow or green discharge							
2.15 Health visit 1 (HomHealthVis1)	0=No visit (default); 1=Visit to health center; 2=Traditional healer; 3=Pharmacy; 4=Private physician; 5=Hospitalized; 66=Other							
2.16 Health visit 2 (HomHealthVis2)								
2.17 Reason visit 1 (HomReasonVis1)	0=No visit (default); 1=Well child visit; 2=Respiratory illness; 3=Earache or ear discharge; 4=Diarrhea, dehydration, vomiting; 5=Fever, 6=Poor appetite or non-specific illness; 7=Skin rash; 8=Accident, trauma; 66=Other							
2.18 Reason visit 2 (HomReasonVis2)								
2.19 Drug 1 (HomDrug1)	0=None (default); 1=Antibiotic; 2=Anti-malarial; 3=Anti-parasitic; 4=Antipyretic medicine; 5=Medicine provided, but type unknown; 66=Other							
2.20 Drug 2 (HomDrug2)								
2.21 Drug 3 (HomDrug3)								

3. Physical examination (Do malaria test if child is reported to have had fever yesterday or today or if the child's temperature today is >38 (°C)

3.1 Respiratory rate /min (mark 999 if not measured). 3.1.1. Rate 1 (HomRespRate1) 3.1.2. Rate 2 (HomRespRate2)

3.2 Temperature (mark 99.9 if not measured) (HomTemperature)..... . °C

3.2.1 Danger signs (tick all) (HomDangerSigns) ☐ [0]None ☐ [1]Not able to drink or breast feed ☐ [2]Vomiting everything ☐ [3]Seizure/convulsion ☐ [4]Severe respiratory distress ☐ [99] Unknown (child not present)

3.3 Malaria rapid test results (RDT): (HomMalariaRDT)

☐ [0] Negative ☐ [1] Positive, P. falciparum ☐ [2] Positive, other malaria ☐ [3] Invalid ☐ [99] Test not done

4. Referral for treatment

4.1 Referred to: (HomReferral)..... ☐ [0] Healthy, no referral needed ☐ [1] Local health centre ☐ [2] Hospital ☐ [66] Other

4.1.1 If other Specify (HomSpecReferral)

4.2 Free comments: (HomComments):

Give the planned ration of the food supplement or soap to the guardian. If a twin, give two rations! Acquire guardian's signature of the receipt of food or soap.

iii. Collector (HomCollector) iii. Monitor (HomMonitor)

iv Date (HomDateCollector) - - 20 iv. Date (HomDateMonitor) - - 20

Page 1 of 1

Appendix 4.2. Morbidity calender

iLiNS-DOSE trial *Participant Code:* |___|___|___|___| (ChildNumber)

Form 17. Weekly Morbidity Calendar, Chichewa (version:2009-12-14)

1. VISIT INFORMATION

Number (code) of visit (when data are collected):.....|___|___|___|

Date of first day of of data collection (day when calendar is left at home):. .|___|___| |___|___| 20 |___|___|

Date of last day of data collection (day preceding next home visit):.....|___|___| |___|___| 20 |___|___|

2. LNS USE AND MORBIDITY DURING THE FOLLOW-UP PERIOD

Tsiku la msabata Day of the week	Write in day (circle Friday)							
Mwana anadya chiponde Child ate LNS Form 18, q2.4								
Mwana anali bwino Child was well								
Anachepetsa zichitochito / kaseweredwe Reduced activity Form 18, q2.5								
Analibe chilakolako chofuna kudya Poor appetite Form 18, q2.6								
Kutsegula mmimba Diarhoea (mark number) Form 18, q2.7, q2.8								
Kusanza Vomiting Form 18, q2.9								
Kutentha thupi Fever Form 18, q2.10								
Kutsokomola Cough Form 18, q2.11, 2.12, 2.13								
Kutuluka mamina Nasal discharge Form 18, q2.14								
Kuonana ndi a chipatala koyamba Health visit 1 Form 18, q2.15-2.21